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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,248	03/29/2004	Alex J. Harvey	AVI-027N	2313

26739 7590 01/22/2007

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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/812,248	HARVEY ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,8-10,33-35 and 40-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8-10,33-35 and 40-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11-3-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 4-7, 11-32 and 36-69 have been canceled. Claims 1-3, 8-10, 33-35 and 40-42 are pending and under consideration in the instant office action.

Support for "blastodermal cell" and "totipotent avian cell" in the amendment filed 11-3-06 is found in original claim 9 and on pg 10, lines 5-7. Please provide support for each and every change in the claims by page and line number or by original claim.

The amendment filed 11-3-06 has an error in the markings of claim 1. The deleted terms "non-lethal" and "gene" are not present in the amendment. It is assumed that the official version of claim 1 is the one provided 11-3-06 despite the marking errors. Please include the entire previous claim in any future amendments with lines through words that are deleted and lines under new words.

Applicant's arguments filed 11-3-06 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This office action is non-final in view of the new inherency arguments made by the examiner in the 102 rejections.

Specification

The application number on pg 19, line 29, will have to be updated upon being allowed or abandoned.

Pg 35, line 16, was amended on 11-3-06 but still has no temperature indicated.

The sentence at the end of the first paragraph on pg 48 was corrected in the amendment filed on 11-3-06.

Claim Rejections - 35 USC § 112

Claims 1-3, 8-10, 33-35 and 40-42 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for integrating a transgene into avian blastodermal cells by electroporating the transgene into the avian blastodermal cells, does not reasonably provide enablement for integrating a transgene into an avian totipotent cell by electroporating the transgene into avian blastodermal cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1 is drawn to producing an integrated transgene in an avian cell comprising introducing a nucleic acid sequence comprising an antibiotic resistance marker into an avian blastodermal cell by electroporating; and allowing the cell to undergo a cellular division; thereby producing an integrated transgene in an avian blastodermal cell. Claim 1 encompasses stably integrating a transgene into totipotent avian blastodermal cells.

Claim 33 is drawn to producing an integrated transgene in a totipotent avian cell comprising introducing a nucleic acid sequence comprising an antibiotic resistance marker gene into a totipotent avian cell by electroporating; and allowing the cell to undergo a cellular division; thereby producing an integrated transgene in a totipotent avian cell.

Naito (J. Poultry Sci., Oct. 2002, Vol. 39, pg 292-301) electroporated blastodermal cells of a chick embryo in vivo with a plasmid encoding GFP and put the cells in culture to under go cellular division (pg 294, "Embryo manipulation and plasmid DNA" "Transfection of stage X blastoderms by electroporation in vivo" and "Embryo culture and detection of gene expression"). Some of the cells inherently have an integrated transgene as claimed because provisional application 60/458699 states electroporation has low integration efficiency (pg 1, second question, third paragraph). In addition, Naito taught GFP expression persisted from day 1 to day 3, which is an indicator that the transgene is stably integrated into the cells of the developing embryo (see pg 48, lines 3-15 of the instant application).

Naito (J. Poultry Sci., Oct. 2003, Vol. 40, pg 319-323) used the method of Naito (2002) to transfect blastodermal cells of a chick embryo in vivo with a plasmid encoding GFP. "Following the electroporation of stage X blastoderm in vivo, a total of 47 chickens were hatched and 29 chickens grew to maturity (Table 2). The introduced DNA was not detected in the sperm samples of the male chickens, and the GFP gene expression was not detected in the embryonic samples of the female chickens" (pg 321, lines 1-5). Naito concludes, "in vivo electroporation of stage X blastoderm can not be expected to integrate the introduced DNA into the chromosomes of the germline cells" (pg 322, last sentence).

Thus, the art at the time of filing did not teach how to integrate a transgene into the genome of blastodermal avian cells by electroporation.

The specification taught electroporating chicken blastodermal cells (CBC). Pg 48, lines 3-19, states:

> "In order to determine whether the transgene had integrated into the chicken genome, 34 green fluorescent CBC colonies were picked up after transfection of BDCS with linearized pOVTV7.4/0.875-IFN-RSV-EGFP and cultured for 96 hours (this is defined as the primary culture). These colonies were dissociated by pipeting method and cultured in a well of 24 well-plate contained STOs and using BDC-CEE medium (see Methods section). After three days culture about 50% of the resulting colonies exhibited green fluorescence in whole colony (Figure 4 A,B)(this is defined as passage one). Others had no green fluorescence. Several undifferentiated homogenous green fluorescent colonies were picked up from the passage one culture, dissociated and cultured on STOs with BDC-CEE medium. A11 colonies exhibited homogenous green fluorescence in this and subsequent passages (Figure 4C, D, E, F). The homogenous green fluorescent colonies were continuously cultured to passage 11 on the 10 centimeter gelatin dishes and the DNA was extracted for southern blot analysis (Figure 10, lane 9). A single band of ~13 kb was detected in Bam HI digested genomic DNA by the IFN probe. With integration, a band larger than 8.5 kb would be expected."

The specification does not provide any indication that totipotent cells of the CBC colonies have the transgene integrated as in claim 33. Without such guidance, it would require those of skill undue experimentation to determine how to overcome the unpredictability in the art, i.e. how to integrate a transgene into the genome of totipotent avian cells.

Wang (Stem Cells, 2006, Vol. 24, pg 1638-1645) taught the method described by applicants (electroporation of CBCs followed by culture in chick embryo extract) and explains why bands larger than 8.5 kb indicate the transgene is integrated into CBC colonies (pg 1641, col. 2, "The puromycin-resistant transgenes are integrated").

Applicants argue Wang (cited above) taught the methods claimed result in DNA integration into totipotent cells on pg 1643, col. 2, "Transgenic BDC-derived...." Applicants' argument is not persuasive. The paragraph in question on pg 1643 states:

> "To identify male chimeras that carry transgenically modified germ cells, qPCR was performed on purified sperm DNA using the 62-bp neomycin primer/probe set. Four semen samples were collected from each chimera at 2-5-day intervals. Several chimeras gave rise to semen samples with a positive qPCR signal, but that was very low and ranged from 0.5%-0.05% positive (data not shown). There were no chimeras in which all four semen samples were positive. Several chimeras had either only one or two positive semen samples. To determine whether samples were giving rise to false positives during DNA processing or qPCR analysis, previously positive semen samples that had been archived by freezing were reextracted and retested. In most cases, positive semen samples retested as positive."

The sperm cells described by Wang in the paragraph above are not totipotent because they are not capable of becoming any other cell of a chicken.

Applicants point to Naito cannot be used as evidence support the examiner's enablement rejection because the teachings of Naito are different than those used in the present case. Applicants' argument is not persuasive. The teachings of Naito indicate some embodiments claimed are not enabled.

Claim Rejections - 35 USC § 102

Claims 1, 3, 9, 10, 33, 35, 41 and 42 remain rejected under 35 U.S.C. 102(b) as being anticipated by Wei (Poultry Sci., 2001, Vol. 80, pg 1671-1678).

Wei electroporated chicken blastodermal cells (CBC) with a plasmid encoding LacZ. The cells were put in culture and allowed to undergo cellular division for 24, 48 or 72 hours (pg 1672, "Isolation and electroporation of CBC"). Some of the cells inherently have an integrated transgene as claimed because provisional application 60/458699 states electroporation has low integration efficiency (pg 1, second question, third paragraph). Any integration, including low integration, meets the limitation of "producing an integrated transgene" or "stably integrated" as claimed. Without evidence to the

contrary, the method of Wei inherently introduces a double stranded break in a nucleic acid because electroporation introduces double stranded breaks into DNA. The method of claim 33 is included because it does not clearly set forth introducing a nucleic acid into a totipotent avian cell because 1) the phrase "producing an integrated transgene in a totipotent avian cell" in the preamble is an intended use and does not have to occur and 2) the phrase "thereby producing an integrated transgene in a totipotent avian cell" indicates introducing a nucleic acid sequence into any avian cell by electroporation and allowing the cell to undergo division are the means to produce an integrated transgene in a totipotent cell.

Upon further review, the nucleic acid described by Wei inherently encoded an antibiotic resistance gene as evidenced by the Miltenyl Biotech map of the pMACS vector also shows the presence of an ampicillin resistance gene.

Claims 1, 3, 9, 10, 33, 35, 41 and 42 remain rejected under 35 U.S.C. 102(b) as being anticipated by Etches (Poultry Sci., 1997, Vol. 76, pg 1075-1083).

Etches electroporated CBC with a plasmid encoding LacZ and put the cells in culture to under go cellular division (pg 1080, "Transfection"). Some of the cells inherently have an integrated transgene as claimed because provisional application 60/458699 states electroporation has low integration efficiency (pg 1, second question, third paragraph). In addition, Etches teaches the absence of the LacZ in tissues from chimeras made with electroporated cells indicates that it is stably integrated into the genome of CBCs "only rarely" (pg 1080, column 2, lines 10-13). Any integration, including low or rare integration, meets the limitation of "producing an integrated

transgene" or "stably integrated" as claimed. Without evidence to the contrary, the method of Etches inherently introduces a double stranded break in a nucleic acid because electroporation introduces double stranded breaks into DNA. The method of claim 33 is included because it does not clearly set forth introducing a nucleic acid into a totipotent avian cell because 1) the phrase "producing an integrated transgene in a totipotent avian cell" in the preamble is an intended use and does not have to occur and 2) the phrase "thereby producing an integrated transgene in a totipotent avian cell" indicates introducing a nucleic acid sequence into any avian cell by electroporation and allowing the cell to undergo division are the means to produce an integrated transgene in a totipotent cell.

Upon further review, plasmid pmiwz used by Etches inherently has a neomycin resistance gene. The neo gene is capable of being excised by the restriction enzyme XhoI. See "Registration Form YG-VE052" from the JCRB GENE Bank website. The "date of list" of the vector is Dec. 1989.

Claims 1, 3, 9, 10, 33, 35, 41 and 42 remain rejected under 35 U.S.C. 102(a) as being anticipated by Naito (J. Poultry Sci., Oct. 2002, Vol. 39, pg 292-301).

Naito electroporated blastodermal cells of a chick embryo in vivo with a plasmid encoding GFP and put the cells in culture to under go cellular division (pg 294, "Embryo manipulation and plasmid DNA" "Transfection of stage X blastoderms by electroporation in vivo" and "Embryo culture and detection of gene expression"). Some of the cells inherently have an integrated transgene as claimed because provisional application 60/458699 states electroporation has low integration efficiency (pg 1, second question,

third paragraph). In addition, Naito taught GFP expression persisted from day 1 to day 3, which is an indicator that the transgene is stably integrated into the cells of the developing embryo (see instant application on pg 48, lines 3-15). Any integration, including low or rare integration, meets the limitation of "producing an integrated transgene" or "stably integrated" as claimed. Without evidence to the contrary, the method of Naito inherently introduces a double stranded break in a nucleic acid because electroporation introduces double stranded breaks into DNA. The method of claim 33 is included because it does not clearly set forth introducing a nucleic acid into a totipotent avian cell because 1) the phrase "producing an integrated transgene in a totipotent avian cell" in the preamble is an intended use and does not have to occur and 2) the phrase "thereby producing an integrated transgene in a totipotent avian cell" indicates introducing a nucleic acid sequence into any avian cell by electroporation and allowing the cell to undergo division are the means to produce an integrated transgene in a totipotent cell.

Upon further review, plasmid pEGFP-N1 used by Naito inherently has a neomycin resistance gene. See the map of "pEGFP-N1" provided with this office action.

Claim Rejections - 35 USC § 103

Claims 1-3, 9, 10, 33-35, 41 and 42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wei (Poultry Sci., 2001, Vol. 80, pg 1671-1678) in view of Nicolas-Bolnet (Poultry Sci., 1995, Vol. 74, pg 1102-1116).

Wei electroporated chicken blastodermal cells (CBC) with a plasmid encoding LacZ. The cells were put in culture and allowed to undergo cellular division for 24, 48 or

72 hours (pg 1672, "Isolation and electroporation of CBC"). Some of the cells inherently have an integrated transgene as claimed because provisional application 60/458699 states electroporation has low integration efficiency (pg 1, second question, third paragraph). Any integration, including low integration, meets the limitation of "producing an integrated transgene" or "stably integrated" as claimed. Without evidence to the contrary, the method of Wei inherently introduces a double stranded break in a nucleic acid because electroporation introduces double stranded breaks into DNA. The method of claim 33 is included because it does not clearly set forth introducing a nucleic acid into a totipotent avian cell because 1) the phrase "producing an integrated transgene in a totipotent avian cell" in the preamble is an intended use and does not have to occur and 2) the phrase "thereby producing an integrated transgene in a totipotent avian cell" indicates introducing a nucleic acid sequence into any avian cell by electroporation and allowing the cell to undergo division are the means to produce an integrated transgene in a totipotent cell. The plasmid used by Wei inherently comprised an antibiotic resistance gene (see 102 above). Wei did not allow the cells to undergo division in the presence of chick embryo extract (CEE).

However, Nicolas-Bolnet taught CEE increased proliferation of chicken pluripotent cells (pg 1107, "Chick embryo extract or fetal bovine serum-free culture").

Thus, it would have been obvious to those skilled in the art at the time the invention was made to electroporate CBCs as taught by Wei and allow the cells to undergo cell division in the presence of CEE as taught by Nicolas-Bolnet. One of ordinary skill would have been motivated to add CEE to the culture medium to provide

growth factors available to blastodermal cells in an embryo and to increase proliferation of blastodermal cells as taught by Nicolas-Bolnet.

Claims 1-3, 9, 10, 33-35, 41 and 42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Etches (Poultry Sci., 1997, Vol. 76, pg 1075-1083) in view of Nicolas-Bolnet (Poultry Sci., 1995, Vol. 74, pg 1102-1116).

Etches electroporated CBC with a plasmid encoding LacZ and put the cells in culture to under go cellular division (pg 1080, "Transfection"). Some of the cells inherently have an integrated transgene as claimed because provisional application 60/458699 states electroporation has low integration efficiency (pg 1, second question, third paragraph). In addition, Etches teaches the absence of the LacZ in tissues from chimeras made with electroporated cells indicates that it is stably integrated into the genome of CBCs "only rarely" (pg 1080, column 2, lines 10-13). Any integration, including low or rare integration, meets the limitation of "producing an integrated transgene" or "stably integrated" as claimed. Without evidence to the contrary, the method of Etches inherently introduces a double stranded break in a nucleic acid because electroporation introduces double stranded breaks into DNA. The method of claim 33 is included because it does not clearly set forth introducing a nucleic acid into a totipotent avian cell because 1) the phrase "producing an integrated transgene in a totipotent avian cell" in the preamble is an intended use and does not have to occur and 2) the phrase "thereby producing an integrated transgene in a totipotent avian cell" indicates introducing a nucleic acid sequence into any avian cell by electroporation and allowing the cell to undergo division are the means to produce an integrated transgene

in a totipotent cell. The plasmid used by Etches inherently comprised an antibiotic resistance gene (see 102 above). Etches did not allow the cells to undergo cellular division in the presence of CEE.

However, Nicolas-Bolnet taught CEE increased proliferation of chicken pluripotent cells (pg 1107, "Chick embryo extract or fetal bovine serum-free culture").

Thus, it would have been obvious to those skilled in the art at the time the invention was made to electroporate CBCs as taught by Etches and allow the cells to undergo cell division in the presence of CEE as taught by Nicolas-Bolnet. One of ordinary skill would have been motivated to add CEE to the culture medium to provide growth factors available to blastodermal cells in an embryo and to increase proliferation of blastodermal cells as taught by Nicolas-Bolnet.

Double Patenting

The objection of claims 5 and 37 under 37 CFR 1.75 as being a substantial duplicate of claims 4 and 36 has been withdrawn because claims 4, 5, 36 and 37 have been canceled.

Conclusion

The prior art made of record and not relied upon remains pertinent to applicant's disclosure.

Wong (1999, Transgenic Animals in Agriculture, ed J.D. Murray, CABI Publishing, pg 117-129) of record.

This office action is non-final.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER